

Non-Nutritive Sweeteners and Bladder Cancer

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We are pleased, but not surprised, that the reanalysis of the National Cancer Institute study by Walker, *et al.*,¹ has yielded the same findings that we reported^{2,3}. Our preliminary analysis showed no evidence of any association between bladder cancer risk and past consumption of artificial sweeteners (AS) in the total study population. However, we noted a slight tendency toward increased risk with increased intensity of use (amount of AS used daily); this trend was much more prominent in the two subgroups chosen before the start of the study for particular attention, i.e., non-smoking females and heavy-smoking males. Walker and his colleagues, using a slightly different statistical methodology, has faithfully reproduced these results.

Our interpretation of these results was that "past AS use has had a minimal effect, if any, on bladder cancer rates." We reported that "inconsistencies in the data suggest that the positive associations may be due to chance, but that it is noteworthy that the subgroups were chosen, *a priori*, to test hypotheses derived from laboratory experiments."³ The Walker interpretation resembles ours, although some differences exist. We feel that either a causal association or chance may be responsible for the positive findings in the subgroups, while the Walker research team favors chance as the explanation. We do not agree with their argument against a causal interpretation based on a "risk score" analysis of our data. Indeed, the findings from two other studies^{4,5} suggest that a causal explanation cannot yet be dismissed.

Walker, *et al.*, claim that "control for a variety of factors through multivariate techniques diminished the plausibility of earlier interpretations" of the subgroup findings. This apparently refers to the lack of any evidence of a relationship between risk and intensity of AS use in either the lowest or highest "risk category," with the groups defined on the basis of a multivariate "risk score." Although this is apparently at odds with the associations seen in our defined high-risk and low-risk groups, the observations are actually compatible with each other. We chose non-smoking, non-occupationally exposed females *a priori* because their baseline risk of bladder cancer is low and there were enough cases to evaluate the effect of AS use. Similarly, we chose heavy-smoking males as a high-risk group *a priori*. Evaluation of the bladder cancer risks of these two groups after the data were collected verified these designations. The baseline risk

of bladder cancer for those in the highest "risk category" in Walker's report does not approach the high level of risk among heavy-smoking males, and the baseline risk of those in the lowest "risk category" does not approach the low level of risk experienced by non-smoking, non-occupationally exposed females. Rather, these "risk category" groupings of study subjects fall in the intermediate range of baseline risks, a range where our analysis also showed no consistent relationships. The failure of Walker's risk score approach to produce groups with either very high or very low baseline risks apparently results from a confusion of variables that are study "effects" with variables that dictate a population's risk. In generating the risk scores they left out the design variables (age and sex) since these "effects reflect only the sampling procedure and not any biological action." They then assumed that the risk scores "summarize the subjects' baseline bladder cancer risks." This is clearly not so. While the design variables do not differentiate between cases and controls, age and gender are among the most potent bladder cancer risk factors. Any procedure which lumps together males and females cannot achieve a group with as low a risk as low-risk females nor a group with as high a risk as high-risk males. Using data from our population-based study, the age-adjusted bladder cancer rate among non-smoking White males was 15.9/10⁵/yr, whereas the corresponding rate for non-smoking White females was 4.6/10⁵/yr.

Whether the findings in the low-risk group reflect chance occurrence or a weak carcinogenic effect of AS will probably not be elucidated through further analyses of our data set. As in most scientific research, the issue is likely to be resolved by independent evaluation of data from other studies. It is noteworthy that two other studies of bladder cancer have reported relative risks of >2.0 and 1.6 associated with AS use in non-smoking females.^{4,5}

Whether the findings in the high-risk group indicate random variation or a cancer promoting activity of AS may be clarified by a more thorough analysis of our data, incorporating other exposures and temporal considerations. This is currently underway and will be emphasized in our final AS report.

Finally, we do not share Walker's rather dour view of the role of epidemiology in assessing low-level risks. Epidemiology is a dynamic and evolving discipline that may overcome some limitations in this area by advances in methodology, including multidisciplinary approaches. Currently being explored are studies of special disease states and risk groups, specific exposure monitors, and biochemical epidemiology. The special risk groups evaluated in our study seem promising as ways to detect low-level and promotional effects of environmental agents. It is important that we continue to encourage the development and refinement of techniques that will clarify relationships that have eluded the traditional approaches of epidemiology.

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Editor's Note: See also different view, p 376, and related editorial, p 335, this issue.

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